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10/582,705	09/12/2007	John Foekens	47675-078US0	6367

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,705	FOEKENS ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *9,10 and 17-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 June 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I, PITX2 in the reply filed on 7/19/2010 is acknowledged. The traversal is on the ground(s) that SEQ ID NOS 250, 251, 372 and 373 correspond to the bisulfite converted methylated and unmethylated versions of the PITX2 sequence of SEQ ID NO: 23 and should be rejoined. This argument is found persuasive. An action on the merits of claims 1-8 and 11-16, PITX2 is set forth below.

Specification

2. The disclosure is objected to because of the following informalities: The specification lacks a "Brief Description of the Drawings" heading.

Appropriate correction is required.

Drawings

3. The drawings are objected to under 37 CFR 1.83(a) because the black and white pictures fail to discern between the “gray” verses “black” plot as described in the specification. Notably, since gray and black are not distinguishable in the black and white drawings provided, the two plots present in these figures cannot be distinguished from each other. See MPEP § 608.02(d).

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as “amended.” If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must

be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action.

The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112 second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a method for "characterizing a cell proliferative disorder of the breast tissues", however the determining step in step c recites a number of additional limitations, including for example "prognosis of said subject". Accordingly, it is not clear whether the methods are directed to "characterizing a cell proliferative disorder", or to determining a prognosis, disease free survival, etc.

The claims are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps that result in the, characterization, or determining

prognosis, or disease free survival, or probability of response to treatment. The claims recite only steps of obtaining a sample and determining methylation status of PITX2. The "wherein" statement in step c merely sets forth a property of the method, but does not indicate how the method accomplishes the objective of characterization, prognosis, etc by merely performing the steps of obtaining a sample and determining methylation. There is no clear nexus between determining methylation status and determining a characterization, prognosis, etc in the claim,. Accordingly, the claims omit the essential step required by the preamble of the claims of providing a characterization, prognosis, etc.

Claim Rejections - 35 USC § 112 - Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-8 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims encompass methods of providing a characterization of a cell proliferative disorder of the breast, a prognosis, a disease free survival, and the probability of response of a subject to one or more treatment regimens that target the estrogen receptor pathway and/or are involved in estrogen metabolism, production, and/or secretion by determining the methylation status of PTIX2 or its regulatory region.

The claims broadly recite the language of "a subject" and therefor encompass such determinations in a human or non-human subject, such as monkeys, rats, dogs, horses, pigs, etc.

The claims broadly encompass treatments that include, but are not limited to estrogen receptor modulators, estrogen receptor down-regulators, aromatase inhibitors, ovarian ablation, LHRH analogues and other centrally acting drugs influencing estrogen production. Accordingly, the claims encompass determining responsiveness to a very wide range of drugs (antisense drugs, ribozymes, antibody therapy, organic and inorganic compounds), which differ in their structure and mechanism of action.

The claims further encompass a significantly broad genus of disorders, including benign and malignant disorders and specifically including ductal carcinoma in situ, lobular carcinoma, colloid carcinoma, tubular carcinoma, medullary carcinoma, metaplastic carcinoma, intraductal carcinoma in situ, lobular carcinoma in situ and papillary carcinoma in situ. These disorders

differ with respect to their symptoms and etiology. The claims also include the analysis of subjects that are estrogen or progesterone receptor positive and negative.

The claims also include methods in which any biological sample from a subject is analyzed for CpG methylation in a PITX2 . The biological sample may be any sample containing PITX2 nucleic acids, including plasma or serum, blood, skin tissue, nipple aspiration fluid, urine, feces, tears or saliva.

The claims include analyzing any sequence in the PITX2 gene which encompasses tens of thousands of nucleotides, for the methylation status of one or more CpG dinucleotides. Additionally, the claims do not set forth how the results of determining the DNA methylation status of the PITX2 genes are used to characterize, prognose, determine disease free survival or responsiveness to therapy for cell proliferative disorder of the breast, and therefore encompass such phenotypic determinations based on either the presence or absence of methylation at any one or more CpG dinucleotides or based on either hypermethylation or hypomethylation of any one or more CpG dinucleotides in the PITX2 genes.

The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The amount of direction or guidance and Presence and absence of working examples:

The specification teaches a study in which disease-free survival and metastasis-free survival was studied regarding the methylation status of the promoter region of the PITX2 gene in node-negative, estrogen receptor positive human breast carcinoma patients treated with

tamoxifen. These findings are limited to an analysis of breast tissue samples and the PITX2 promoter region. However, due to the lack of discernability regarding "grey" vs "black" plots in the figures, one cannot assess the outcome of such study.

No working examples are provided in which a characterization, prognosis, disease free survival, or response to estrogen therapy is predicted in non-human subjects.

No working examples are provided in which a characterization, prognosis, disease free survival, or response to estrogen therapy is predicted by assaying for methylation status in cell lines, blood samples, urine samples, plasma samples, skin biopsy samples, etc.

No working examples are provided in which outcome of non-tamoxifen therapy is predicted based on PITX2 methylation status.

No working examples are provided in which a characterization, prognosis, disease free survival, or response to estrogen therapy is predicted for cell proliferative disorders of the breast other than node-negative, estrogen receptor positive breast carcinomas.

The state of the prior art and the predictability or unpredictability of the art:

While methylation status is known to effect gene expression, there is no per se art recognized association between methylation status and response to any estrogen related therapy for any breast tissue cell proliferative disorder. The predictability of correlating methylation status to the various claimed phenotypes is affected by such factors as the identity of CpG dinucletoides analyzed as well as the type of sample used. In particular, the unpredictability of predicting responsiveness to therapy by assaying for PITX2 methylation at any CpG dinucleotide, as well as the unpredictability of extrapolating the results from one type of therapy

to another type of therapy, are corroborated by the teachings in the following art, which includes applicants own work. .

Martens (Martens et al; Cancer Research. 2005. 65(10): 4101-4107) teaches the results of a study of the methylation status of 117 genes, including the PITX2 gene, in 200 steroid hormone receptor responsive tumors in patients who received tamoxifen as first-line treatment for recurrent breast cancer. Martens did not observe an association between methylation status of PITX2 and response to treatment(see Supplemental Tables 1 and 2). Martens (page 4101, col. 2) teaches that "(f)rom a biological point of view, however, first-line single agent endocrine therapy in patients with recurrent breast cancer is an excellent setting to study response to therapy because it is less subject to prognostic influences unavoidably present when a similar study would be done in the adjuvant setting." In discussing the variation in results reported therein as compared to those of Widschwendter, Martens (page 4106, col. 1) states that the "reasons for the differences between that study and ours could be manifold including differences in study design (adjuvant versus first-line treatment), in the CpG sites analyzed, in the technology used, or in size or composition of the tissue collections used. Due to the heterogeneity of the cohorts and the likely confounding influence of steroid hormone receptor status, and different treatment modalities, the results of the study of Widschwendter et al are difficult to interpret." Thus, Martens teaches that while it is possible that there may be a difference in results between adjuvant therapy and first line therapy, it is equally possible that any differences in results may be due to a number of other factors *including the identity of the CpG sites analyzed, the tissue sample analyzed and the steroid receptor status of the breast cancer analyzed.* With regard to the teachings of Martens, Nimmrich (Nimmrich et al; Breast Cancer Research and Treatment.

2008. 111:429-437) teaches that "earlier work from our group in clinical specimens did not find *PITX2* DNA-methylation to be associated with intrinsic tamoxifen resistance in metastatic breast cancer" (page 430). At page 434, Nimmrich teaches that in the previous retrospective study of Martens, "we did not find DNA-methylation of PITX2 of the primary tumor to be associated with tamoxifen response (given as a first-line single endocrine agent) in metastatic breast cancer. Nimmrich studied DNA-methylation of the PITX2 gene in untreated lymph node-negative hormone receptor positive breast cancer patients. The authors found that hypermethylation of PITX2 was associated with a poor prognosis and disease progression in these patients. Nimmrich also clarifies the distinction between a marker that is prognostic and markers that are predictive of response to treatment, stating that "a prognostic factor is not necessarily also a predictive marker, or vice versa" (page 434). Nimmrich also acknowledges that differences in methylation results may occur between early stage and advanced breast cancer due to the differences in tumor biology (page 434). The teachings of Nimmrich support the unpredictability of extrapolating the results obtained with one type of breast tissue proliferative disorder to other types of breast tissue proliferative disorders (e.g., early stage breast cancer as compared to late stage, metastatic breast cancer), and with one type of therapy to other types of therapy (e.g., primary treatment with tamoxifen as compared to adjuvant treatment of recurrent cancer with tamoxifen).

The claims further broadly encompass methods in which any sample type such as serum/plasma, urine, brain tissue, saliva, is analyzed for the methylation status of CpGs. However, it is relevant to point out that it is well accepted in the art that gene expression and methylation patterns may vary significantly between tissue. For example, Van Criekinge (PGPUB 2009/0215709; para [0009]) teaches that "Genes that are hypermethylated in tumor

cells are strongly specific to the tissue of origin of the tumor." However, the specification does not teach the methylation pattern of the PITX2 gene in blood samples, spinal cord, lymphatic fluid, urine, feces, or tears etc from patients having a breast tissue proliferative disorder. Accordingly, it is highly unpredictable as to whether the results obtained in one sample type, such as primary breast tissue, can be extrapolated to other tissue types.

Additionally, the claims broadly encompass the above listed phenotypic determinations in any human or non-human subject. However, the specification is silent with regard to whether the methylation status of PITX2 in humans are the same as those present in non-human organisms, such as mice, cats, dogs, etc. Regarding the unpredictability of correlating the methylation status results obtained in humans to non-human organisms it is relevant to point out that Ehrlich (Ehrlich et al; Oncogene 2002. 21: 5400-5413) teaches that there is considerable differences in the amounts and distribution of DNA methylation among different vertebrate tissues because DNA methylation is not only species-specific but also tissue-specific (p. 5400 last paragraph). Therefore, since the distribution of DNA methylation varies between species it is not predictable that the same methylation status differences observed in one species is correlative in another species. Additionally, Nimmrich teaches "(f)rom a biological point of view, the role of PITX2 DNA-methylation and cancer is unknown" (page 435, col. 1).

It is further unpredictable as to whether any single CpG or any combination of any CpGs in any region of the PITX2 gene can be analyzed for the methylation status as indicative of the broadly claimed phenotypes. The claims do not require any type of comparison step with a control, non-cancer or non-responsive sample, and thereby include methods in which the presence or absence of methylation at a single CpG is detected as predictive of any of the

broadly claimed phenotypes. However, the specification has not established such an association between any single CpG and characterization, disease free survival, prognosis or response to any treatment. Further, the results in the specification appear to be limited to the regions cited above which consist of portions of the promoter region of the PITX2. It is well known in the art that different regions of a gene may be methylated in cancer tissues and in normal tissues, such that the occurrence of any one methylated CpG alone is not necessarily predictive of phenotype, let alone, characterization, disease free survival, prognosis or response to any treatment of a cell proliferative disorder of the breast tissue. The effect of methylation may vary depending on the location of the methylated CpG. For example, methylation of CpGs present in the promoter region of a gene may alter gene expression, whereas methylation of CpGs in coding sequences of a gene may not. Regarding the unpredictability of applying methylation results to the prediction of a phenotype, it is relevant to poin out that Ushijima (Nature Reviews. 2005. 5: 223-231) teaches that "interpretation of differential methylation has proven difficult because the significance of methylation alterations depends on the genomic region, and functions of the CpG islands at specific sites have not been fully clarified" (see abstract). Ushijima teaches that both hypermethylation and hypomethylation are associated with the occurrence of cancer (page 223). Ushijima (page 223) also teaches that "it has become recognized that methylation in cancer cells frequently occurs in CGIs outside promoter regions, which do not repress gene transcription, and also in promoter CGIs of genes that cannot be regarded as tumour-suppressor genes. Even in normal cells, methylation of specific CGIs frequently occurs. Therefore, to identify novel tumour suppressor genes silenced in cancer cells by CGI methylation it is necessary to carefully select the particular CGIs to be included in the analysis."

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

While methylation status is known to effect gene expression, there is no per se art recognized association between methylation status and response to any estrogen related therapy for any breast tissue cell proliferative disorder. The predictability of correlating methylation status to the various claimed phenotypes is affected by such factors as the identity of CpG dinucletoides analyzed as well as the type of sample used.

Although the specification teaches a study in which disease-free survival and metastasis-free survival was studied regarding the methylation status of the promoter region of the PITX2 gene in node-negative, estrogen receptor positive human breast carcinoma patients treated with tamoxifen, this study was limited to an analysis of breast tissue samples and the PITX2 promoter region. Additionally, due to the lack of discernability regarding "grey" vs "black" plots in the figures, one cannot assess the outcome of such study, accordingly, the skilled artisan would be required to perform such as study to determine the predictability of the methylation status of PITX2 as a marker for the various claimed phenotypes.

Additionally, the skilled artisan would be required to perform extensive trial and error experimentation to determine if a characterization, prognosis, disease free survival, or response to estrogen therapy is possible in non-human subjects, for methylation status in cell lines, blood samples, urine samples, plasma samples, skin biopsy samples, etc., for outcome of non-

tamoxifen therapy based on PITX2 methylation status, as well as for cell proliferative disorders of the breast other than node-negative, estrogen receptor positive breast carcinomas.

There is no specific guidance provided in the specification as to the types of cells or tissues, other than primary breast tissue, which one would be expected to show a change in methylation status in subjects having breast cancer. One cannot determine which tissues or biological fluids will contain PITX2 nucleic acids showing an altered methylation pattern as predictive of response to therapy without experimentation. The specification does not provide sufficient teaching for one of skill in the art to determine which of the thousands of particular CpGs in the PITX2 gene are to be analyzed as predictive of the claimed phenotypes, including response to therapy or prognosis of breast proliferative disorders. The claims encompass methods in which any single CpG or any combination of CpGs in any coding or non-coding region of the PITX2 gene is analyzed for methylation status such that a characterization, prognosis or prediction of outcome of estrogen related therapy is "afforded". The claims include analyzing any coding or non-coding sequence of the PITX2 gene or its regulatory region for methylation status. However, it appears that the specification analyzed only a region of the promoter for methylation status. Insufficient guidance is provided as to which regions outside of the assayed promoter regions could be analyzed to determine if an increase or decrease level of methylation is correlated with the claimed phenotypes let alone prognosis or estrogen therapy outcome. Additionally, extensive experimentation would be required to identify additional organisms, tissues, and therapies in which PITX2 methylation is correlated with the claimed phenotypes. While methods for determining CpG methylation status are known in the art, such methods provide only the general guidelines that allow researchers to randomly determine if

particular CpGs or regions of a gene containing CpGs are methylated. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional organisms and tissues/fluids and particular CpGs in which an altered CpG methylation status will be correlated with the claimed phenotypes.

Given the art accepted unpredictability in the associated field, the experimentation would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

5. No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Mondays from 9:00 AM to 1:00 PM, and Tuesdays & Thursdays from 9:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571) 272-0731. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Jehanne Sitton/
Primary Examiner
Art Unit 1634